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A MATCHED ANALYSIS OF DIABETES MELLITUS AND HERBICIDE EXPOSURE IN VETERANS OF OPERATION RANCH HAND

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14. ABSTRACT

We studied diabetes in Air Force veterans exposed to Agent Orange and its contaminant 2,3,7,8 tetrachlorodibenzo-p-dioxin (dioxin) during the Vietnam War. The index subjects of the Air Force's ongoing 20-year prospective epidemiological study were veterans of Operation Ranch Hand, the unit responsible for aerial herbicide spraying in Vietnam from 1962 to 1971. Other Air Force veterans who served in Southeast Asia during the same period but were not involved with spraying herbicides serve as Comparisons. The median dioxin level in the Ranch Hand group was 12.2 parts per trillion (ppt) [range: 0.6 to 617.8 ppt] and the median dioxin level in the Comparison group was 4.0 ppt (range: 0.4 to 54.8 ppt). We estimated relative risk in matched pairs, overall, and by dioxin exposure category, matched on year of birth, family history of diabetes, race, military occupation, and percent body fat while in Vietnam (to within 1%). We found the risk of diabetes significantly increased among Ranch Hands (relative risk=1.4, 95% CI 1.0 to 1.8, p=0.02) and a borderline significantly increased risk in the High exposure category (relative risk=1.6, 95% CI 1.0 to 2.5, p=0.06). These data also suggest that a previously observed "check mark" pattern of decreased risk at low dioxin levels and an increased risk at high levels may have been artifactual.

15. SUBJECT TERMS

Diabetes mellitus, Agent Orange, dioxin, Vietnam veterans, herbicides.

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1. INTRODUCTION

An analysis of type 2 diabetes mellitus and exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin) in Air Force veterans of Operation Ranch Hand, the unit responsible for aerially spraying Agent Orange and other dioxin-contaminated herbicides in Vietnam, found an increased risk of diabetes in the subgroup with the highest serum dioxin levels (Henriksen et al., 1997). A recent review of the cumulative evidence in the scientific literature led the National Academy of Sciences (NAS) to conclude that there was limited/suggestive evidence of an association between exposure to the herbicides used in Vietnam or the contaminant dioxin and type 2 diabetes (Institute of Medicine, 2000).

Although the risk of diabetes was increased in Ranch Hand veterans in the highest exposure category, there was no overall increase in diabetic risk and the risk was decreased among those with background levels of serum dioxin. We have named this the check mark pattern and have been unable to explain it with standard covariate-adjusted statistical modeling. Since it was first observed in this study in 1991, the pattern has remained a source of controversy. We present a reanalysis of the Ranch Hand data in an attempt to understand the check mark pattern.

2. METHODS

The details of study design and subject selection are published elsewhere (Wolfe et al., 1990). The study seeks to determine whether veterans of Operation Ranch Hand (the personnel tasked with spraying operations during the Vietnam conflict) have experienced adverse health and whether those health effects, if they exist, can be attributed to exposure to herbicides or their dioxin contaminant. Ranch Hand veterans were exposed to herbicides during flight operations and maintenance of the aircraft and herbicide spray equipment. The study compares the current health and cumulative mortality experience of Ranch Hand veterans with a comparison group of other Air Force veterans who served in Southeast Asia during the same period (1962 to 1971) that the Ranch Hand unit was active and who were not involved with spraying herbicides. Comparisons were matched to Ranch Hands on age, race and military occupation. All Ranch Hand veterans were male. The study includes periodic analyses of non-combat mortality, in-person interviews and physical examinations. Physical examinations were conducted in 1982, 1985, 1987, 1992, and 1997 and an additional examination is planned for 2002.

In 1987, blood from willing participants was collected and assayed for dioxin (Patterson Jr et al., 1987). Participation was voluntary and consent forms were signed at the examination site. Veterans with no quantifiable dioxin result in 1987, those who refused in 1987 and subjects new to the study were also asked to give blood for the assay at the 1992 examination. Similarly, veterans with no quantifiable dioxin results in 1987

and 1992, those who refused in 1987 and 1992, and veterans new to the study were also asked to give blood for assay at the 1997 examination. Of the 2,121 veterans who attended the 1997 physical examination, dioxin measurements were made for 2,101 veterans (99.1%). Of the 2,101, the 1987 dioxin level was measured for 1,644 (78.2%); the 1992 dioxin level was measured for 312 (14.9%) and the 1997 dioxin level was measured for 139 (6.6%). Four (0.2%) received a detectable result less than the limit of quantitation (LOQ), 2 (0.1%) received no result (due to a failure of one or more laboratory quality control checks and insufficient sample to repeat the assay), and 143 (6.8%) received results below the limit of detection (LOD). Dioxin results less than the LOD (LOQ) were assigned the value LOD (LOQ) divided by the square root of 2 (Hornung and Reed, 1990). The serum dioxin measurements were done with high-resolution gas chromatography/high resolution mass spectrometry. The between assay coefficient of variation at three different concentrations of dioxin ranged from 9.4% to 15.5%.

We reviewed medical records and laboratory results to determine diabetic status. Veterans who attended at least one examination and had a verified history of diabetes by medical diagnosis or exhibited a 2-hour post-prandial glucose laboratory value of 200 mg/dl or greater were classified as diabetic. Veterans not meeting these criteria were defined as non-diabetic.

Physician-diagnosed diabetes cases included for analysis were diagnosed during the post-Vietnam period from the end of the veteran's last tour of duty to December 31,

2000. We report cumulative post-service diabetes. Each diagnosis was verified from medical records and may represent a diagnosis at any of the five physical examinations or by the veteran's personal physician. Every veteran who attended at least one examination, regardless of his current vital status, was considered for inclusion in the analysis.

We excluded from all statistical analyses veterans with a history of diabetes prior to service in Southeast Asia and those with no dioxin measurement. Table 1 shows sample size reductions by group (Ranch Hand, Comparison).

Table 1. Sample Size Reduction by Group

	Ranch Hand	Comparison	Total
Fully Compliant at any Exam	1,111	1,571	2,682
Missing Dioxin*	(90)	(125)	(215)
No blood draw result†	(4)	(10)	(14)
Missing a limit of detection	(1)	(0)	(1)
Diabetes prior to service in Southeast Asia	(2)	(1)	(3)
Net	1,014	1,435	2,449

* Refused the blood draw or medically deferred from giving blood.
† Due to a failure of one or more quality control checks and insufficient sample to repeat the assay.

We estimated the initial dioxin dose at the end of the tour of duty in Vietnam in Ranch Hands having current dioxin levels above background using a constant half-life of

8.7 years (Michalek et al., 1996) and assigned each veteran to one of four exposure categories, named "Comparison", "Background", "Low" and "High", according to his group, current dioxin level (D) and initial dioxin level (I), defined in Table 2. The cut point separating the Low and High categories (94 ppt) is the median initial dioxin level among all Ranch Hands having current dioxin levels greater than 10 ppt. Table 2 shows sample sizes by dioxin category.

Table 2. Exposure Category Definition and Associated Sample Sizes

Dioxin Category	Definition*	Sample Size
Comparison		1,435
Ranch Hand		
Background	D≤10	442
Low	D>10 and I≤94	286
High	D>10 and I>94	286
Total		2,449

* D=current dioxin, I=initial dioxin, in parts per trillion.

We defined percent body fat (PBF) as PBF=1.26×BMI-13.305, where BMI is the body mass index [weight (kg) divided by the square of height (m)] (Knapik et al., 1983).

We estimated relative risk (RR) using main-effects covariate-adjusted proportional hazards model, adjusted for year of birth, race, military occupation (officer, enlisted flyer, enlisted ground), family history of type 2 diabetes (in first-order relatives), and PBF during their tour of duty in Southeast Asia. We contrasted all Ranch Hands with all Comparisons and each of the three Ranch Hand exposure categories (Background, Low, High) with Comparisons.

We individually matched Comparisons to Ranch Hands, one-to-one, based on year of birth, race, military occupation (officer, enlisted flyer, enlisted ground), family history of type 2 diabetes (in first-order relatives), and PBF during their tour of duty in Southeast Asia. We estimated the relative risk and confidence interval and tested the hypothesis that RR=1 using algorithms derived for one-to-one matched sets (Rothman and Greenland, 1998) in the entire cohort and by dioxin exposure category.

3. RESULTS

Demographic characteristics of all veterans are presented in Table 3. Ranch Hands in the High dioxin category were younger than those in the Low and Background categories. Most of the Ranch Hands in the High dioxin category were enlisted ground personnel and those in the Background category are predominantly officers. The median (and range) of initial dioxin levels, in ppt, in the Low and High categories were, Low: 52.7 (27 to 94), High: 197.8 (94 to 3,290).

In an unmatched analysis, we found that the risk of diabetes in Ranch Hand veterans was not significantly different from the risk in Comparison veterans (RR=1.0, 95% CI 0.8 to 1.2, not shown in any table). Unmatched analyses of diabetes and dioxin category are summarized in Table 4. The risk of diabetes in the Low (RR=1.1) and High (RR=1.3) dioxin categories was increased (Table 4), and the risk in the Background category was decreased (RR=0.7).

Comparisons were matched to Ranch Hands within each of the three Ranch Hand exposure categories with PBF in Vietnam matched to within 3%, 2% and 1%. Matched pairs are summarized in Table 5. The median dioxin level among the 95 Ranch Hands in the High category matched to within 1% to Comparisons was 47.0 ppt (Range 21.8 to 544.7) and the median among their matched Comparisons was 4.0 ppt (Range 0.7 to 14.8). PBF was decreased among Ranch Hands in the Background category (mean=17.2) relative to the Low (mean=18.8) and High (mean=19.0) categories.

Table 3. Distribution of Dioxin and Demographic Characteristics by Dioxin Exposure Category

Characteristic	Comparison	Ranch Hand		
		Background	Low	High
Dioxin*				
median	4.0	5.7	52.7	197.8
range	0.4 to 54.8	0.6 to10	27 to 94	94 to 3,290
Birth year				
Mean	1938.5	1937.4	1937.0	1941.1
Percent Body Fat				
Mean (SD)	18.2 (3.8)	17.1 (3.4)	18.6 (3.9)	18.7 (4.1)
Family history of diabetes (%)	30.2	27.4	26.9	37.4
Black (%)	6.3	5.2	8.4	4.9
Occupation:				
Officer (%)	38.1	60.2	38.1	2.5
Enlisted Flyer (%)	15.7	12.4	21.3	20.6
Enlisted Ground Crew (%)	46.2	27.4	40.6	76.9

*Current dioxin levels in the Comparison and Background categories, initial dioxin in the Low and High categories, in parts per trillion.

Table 4. Diabetes by Dioxin Exposure Category*.

Condition	Comparison (N=1,435)	Ranch Hand		
		Background (N=442)	Low (N=286)	High (N=286)
Diabetes				
Number (%)	257 (17.9)	48 (10.9)	61 (21.3)	70 (24.5)
RR†	1.0	0.7	1.1	1.3
95% CI		(0.5, 1.0)	(0.8, 1.4)	(1.0, 1.7)

*Unmatched.
†From a proportional hazards regression model adjusted for occupation, race, family history of diabetes, birth year, and percent body fat while in Southeast Asia.

A matched analysis of Ranch Hands and Comparisons without regard to dioxin level (Table 6) found the risk of diabetes significantly increased with PBF matched to within 1%; RR=1.4, 95% CI 1.0 to 1.8, p=0.02. Of the 398 matched Ranch Hands, 84 (21.1%) were diabetic, and of the corresponding 398 matched Comparisons 62 (15.6%) were diabetic.

Matched analysis of diabetes by dioxin exposure category (Table 7) found the risk of diabetes borderline significantly increased in the High exposure category after matching PBF in Vietnam to within 1%. Of the 95 matched Ranch Hands in the High category 25 (26.3%) were diabetic and 16 (16.8%) of their 95 matched Comparisons were diabetic; RR=1.6, 95% CI 1.0 to 2.5, p=0.06.

Table 5. Matched set descriptive statistics

a) Percent body fat matched to within 3%

	Background (406 matched pairs)		Low (255 matched pairs)		High (268 matched pairs)	
	C*	R*	C*	R*	C*	R*
Dioxin (Median)	4.0	5.7	3.9	14.8	4.0	45.8
(Range)	0.4, 26.6	0.6, 10	0.6, 16.1	10, 26.6	0.4, 54.8	18.0- 544.7
Initial dioxin (Median)				51.6		195.3
(Range)				27.2, 94.1		94.1- 2,457
Percent body fat (Mean)	17.2	17.1	18.4	18.4	18.5	18.5
Birth year (Mean)	1937.7	1937.6	1937.7	1937.7	1941.3	1941.3
Black (%)	3.7	3.7	6.3	6.3	3.7	3.7
Family history of diabetes (%)	25.4	25.4	25.5	25.5	35.8	35.8
Enlisted Flyer (%)	11.1	11.1	20.8	20.8	18.3	18.3
Enlisted Ground Crew (%)	27.6	27.6	40.8	40.8	79.1	79.1

*C = Comparison, R = Ranch Hand

Table 5. (Continued)

b) Percent body fat matched to within 2%

	Background (283 matched pairs)		Low (183 matched pairs)		High (180 matched pairs)	
	C*	R*	C*	R*	C*	R*
Dioxin (Median)	4.1	6.1		14.6	4.0	49.4
(Range)	0.4, 16.0	0.6, 10		10.0, 26.6	0.5, 54.8	18.0, 544.7
Initial dioxin (Median)				51.2		200.7
(Range)				27.2, 94.1		94.1, 2,457
Percent body fat (Mean)	17.2	17.1	18.3	18.3	18.5	18.4
Birth year (Mean)	1937.6	1937.6		1937.6	1940.8	1940.9
Black (%)	4.2	4.2	C*	5.5	4.4	4.4
Family history of diabetes (%)	23.3	23.3	4.0	28.4	36.7	36.7
Enlisted Flyer (%)	9.9	9.9	0.6, 16.1	23.0	19.4	19.4
Enlisted Ground Crew (%)	28.6	28.6		38.8	78.3	78.3

*C = Comparison, R = Ranch Hand

Table 5. (Continued)

c) Percent body fat matched to within 1%

	Background (161 matched pairs)		Low (104 matched pairs)		High (95 matched pairs)	
	C*	R*	C*	R*	C*	R*
Dioxin (Median)	4.1	6.3	4.0	14.6	4.0	47.0
(Range)	0.4, 17.3	0.6, 10	0.6, 9.5	10.0, 25.6	0.7, 14.8	21.8, 544.7
Initial dioxin (Median)				51.5		197.9
(Range)				27.2, 93.8		94.1, 2,457
Percent body fat (Mean)	17.2	17.2	18.9	18.8	18.9	19.0
Birth year (Mean)	1937.0	1937.0	1936.8	1936.8	1941.1	1941.1
Black (%)	5.6	5.6	5.8	5.8	6.3	6.3
Family history of diabetes (%)	24.8	24.8	29.8	29.8	36.8	36.8
Enlisted Flyer (%)	11.2	11.2	21.2	21.2	16.8	16.8
Enlisted Ground Crew (%)	31.1	31.1	35.6	35.6	81.1	81.1

*C = Comparison, R = Ranch Hand

Table 6. Matched analysis of diabetes and herbicide exposure

a) PBF matched to within 3% (1,010 matched pairs)

Diabetic (%)			
Comparison	Ranch Hand	Relative Risk (95% CI)	p-value
168 (16.6)	168 (16.6)	1.0 (0.8, 1.2)	1.0

b) PBF matched to within 2% (710 matched pairs)

Diabetic (%)			
Comparison	Ranch Hand	Relative Risk (95% CI)	p-value
122 (17.2)	127 (17.9)	1.0 (0.8, 1.3)	0.70

c) PBF matched to within 1% (398 matched pairs)

Diabetic (%)			
Comparison	Ranch Hand	Relative Risk (95% CI)	p-value
62 (15.6)	84 (21.1)	1.4 (1.0, 1.8)	0.02

Table 7. Matched dioxin exposure category analyses

a) Percent body fat matched to within 3%

		Diabetic (%)			
Exposure Category	Matched Pairs	Comparison	Ranch Hand	Relative Risk (95% CI)	p-value
Background	406	55 (13.6)	47 (11.6)	0.9 (0.6, 1.2)	0.36
Low	255	51 (20.0)	50 (19.6)	1.0 (0.7, 1.4)	0.91
High	268	52 (19.4)	62 (23.1)	1.2 (0.9, 1.6)	0.27

b) Percent body fat matched to within 2%

		Diabetic (%)			
Exposure Category	Matched Pairs	Comparison	Ranch Hand	Relative Risk (95% CI)	p-value
Background	283	41 (14.5)	39 (13.8)	1.0 (0.7, 1.4)	0.79
Low	183	36 (19.7)	36 (19.7)	1.0 (0.7, 1.4)	1.0
High	180	36 (20.0)	43 (23.9)	1.2 (0.8, 1.7)	0.31

c) Percent body fat matched to within 1%

		Diabetic (%)			
Exposure Category	Matched Pairs	Comparison	Ranch Hand	Relative Risk (95% CI)	p-value
Background	161	23 (14.3)	27(16.8)	1.2 (0.7, 1.9)	0.50
Low	104	20 (19.2)	25 (24.0)	1.3 (0.8, 1.9)	0.32
High	95	16 (16.8)	25 (26.3)	1.6 (1.0, 2.5)	0.06

4. DISCUSSION

In an unmatched analysis, we found no increase in the risk of diabetes in Ranch Hand veterans based on diabetes prevalence to December 31, 2000. Without matching, the diabetes risk was, however, significantly increased in the High exposure category and decreased in the Ranch Hand Background category. This pattern paralleled that observed in our earlier analysis (Henriksen et al., 1997) and replicated a phenomenon we named the "check mark" pattern. An analysis based on individual one-to-one matching on year of birth (to within one year), race, military occupation, family history of diabetes, and PBF during service in Southeast Asia (to within 1%), found a significantly increased risk of diabetes in all Ranch Hand veterans, an increased risk in all three Ranch Hand exposure categories, and a borderline significant increase in the High category.

These analyses were motivated by a "check mark" pattern of decreased diabetes risk in Ranch Hands with background dioxin levels, increased risk in those in the High dioxin category, and no overall difference in risk between Ranch Hands and Comparisons. In presentations of these data to peer review groups, including the National Academy of Sciences, the suggestion was made that lack of adjustment for important risk factors may account for the pattern. We found that the check mark pattern failed to appear after individual matching on percent body fat while in service in Southeast Asia (to within 1%), and perfect matching on family history of diabetes, race, and military occupation; the relative risk was increased overall and in all three dioxin exposure categories. This suggests that residual confounding, not accounted for by the

proportional hazards model, may have biased the overall relative risk towards unity and the relative risk in the background exposure category towards a value less than 1.0. It is not yet known how residual confounding may have produced the check mark pattern in the unmatched covariate-adjusted analyses.

The strengths of our study include high participation rates, a Comparison population closely matched to the index population, and ten years of follow-up. Active quality control incorporating double blind entry of data with discordances referred for third-party review and medical review of potential outliers reduced errors that would bias the study toward the null result. The study is limited by the serum dioxin measurement. The serum dioxin measurements are accurate (Michalek et al., 1996) and correlated with skin exposure to herbicide in Vietnam (Michalek et al., 1995), but were made up to 30 years after exposure. The accuracy of our initial dose estimate is unknown.

Based on cumulative diabetes prevalence to December 31, 2000, an unmatched analysis of diabetes and dioxin category using covariate-adjusted proportional hazards regression models found an increased diabetes risk among Ranch Hands in the High exposure category, a decreased risk among Ranch Hands in the Background category, and no overall increase in risk in the Ranch Hand cohort. With Ranch Hand and Comparisons individually matched on five risk factors and close matching on PBF we found a borderline significantly increased diabetes risk in the High category and an overall significantly increased risk in the entire Ranch Hand cohort. These results appear consistent with the hypothesis that diabetes is adversely related to herbicide or dioxin

exposure in Ranch Hand veterans and suggest that the check mark pattern may be an artifact of confounding.

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